amended claims 40-49 are in compliance with the requirement under 35 U.S.C. §112, second paragraph. Applicants respectfully request the rejection be withdrawn.

With regard to the rejection to claims 50-57, applicants point out that these claims do not recite the alleged term "dysfunctional state." Rather, the term was cited in claims 58-64. In the interest of expediting the patent application process in a manner consistent with promoting and facilitating licensing opportunities, claims 58-64 have been canceled, rendering the rejection regarding the term "dysfunctional state" moot. Applicants respectfully request the rejection be withdrawn.

Rejection Under 35 U.S.C. §102(e)

Claims 40-64 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Patent No. 5932540 to Hu et al. (hereinafter the "'540 patent"). The anticipation rejection is based on inherency. The Office Action reasons that the methods of administration disclosed in the '540 patent use identical products to the methods claimed in the instant application, and therefore concludes that it is an inherent property of the methods of the '540 patent to stimulate tyrosine phosphorylation of Flt4 as presently claimed. Applicants respectfully traverse.

To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently. *Hazani v. U.S. Int'l Trade Comm*, 44 USPQ2d 1358 (Fed. Cir. 1997). If the prior art reference does not expressly set forth a particular element of the claim, that reference still may anticipate if that element is necessarily present in the reference, and that it would be so recognized by persons of ordinary skill. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 20 USPQ2d 1746, 1749-50 (Fed. Cir. 1991); *In re Robertson,* 49 USPQ2d 1949 (Fed. Cir. 1999). In the present case, the inherency argument of the Office would require that the '540 patent teaches a method of using the subject polypeptide that would necessarily result in the stimulation of the tyrosine phosphorylation of a Flt4 tyrosine kinase receptor in a Flt4-expressing cell. Applicants submit that it is not the case.

The '540 patent describes a human VEGF2 polypeptide (SEQ ID 2) based on its sequence homology to VEGF, a known angiogenic factor specific to vascular endothelial cells. Throughout the specification, the putative functions of VEGF2 are mainly based

on its limited sequence homology to VEGF and what have been known about VEGF's role in angiogenesis and related biological conditions. For example, the '540 specification postulates that VEGF2 can be used for stimulating angiogenesis, wound-healing or growth of damaged bones, all of which have been known to involve VEGF activities. See "Summary of the Invention" at columns 2-3; and general descriptions at columns 16-17 of the '540 patent. The '540 patent therefore does not describe or suggest that VEGF2 is a ligand to the Flt4 tyrosine kinase receptor (to which, as discussed below, VEGF does not bind at all), that Flt4 is not expressed in all endothelial cells expressing VEGF receptors, and that VEGF2 can stimulate the tyrosine phosphorylation of Flt4 in Flt4 expressing cells.

Conversely, the present invention resulted from applicants' active searching for ligand(s) of the Flt4 receptor, and for uses thereof in modulating Flt4 activities. As discussed in the present application, Flt4 receptor was previously identified as an orphan receptor sharing certain sequence homology to the two VEGF receptors, Flt1 and Flk1 (also known as KDR). While VEGF is a high-affinity ligand for Flt1 and Flk1, it does not bind or activate Flt4. Specification at page 2, lines 14-24 and page 4, lines 6-7. In other word, prior to the present invention, no Flt4 ligand had been identified, much less ligand-induced tyrosine phosphorylation of the Flt4 receptor. Moreover, at the time of the present application, Flt4 receptor had been found associated with certain, but not all, endothelial cells. For example, as discussed in the present application at page 3, lines 5-15, Flt4 is expressed only in adult human lymphatic endothelia, but not in arteries, veins and capillaries. Thus, Flt4 and its ligand(s) act differently from the known VEGF and VEGF receptors. And processes involving VEGF/VEGF receptor signaling pathway (such as vascular endothelial cell proliferation) do not necessarily involve activation of the Flt4 receptors.

Applicants submit that the present invention as claimed is directed to methods for stimulating the phosphorylation of the Flt4 receptor and methods for promoting growth of Flt4-expressing endothelial cells. The invention is based on the discovery, for the first time, of a Flt4 ligand designated VRP. The present application describes not only the DNA and protein sequences of VRP, but also its functions of binding to, and stimulating the phosphorylation of, the Flt4 receptor. As described in the specification and further

discussed above, the Flt4 receptor behaves differently from the VEGF receptors Flt1 and Flk1. Furthermore, applicants point out that in addition to its binding to the Flt4 receptor, VRP (also called VEGF-C) has been shown to bind to the VEGF receptor Flk1 as well. Applicants submit herewith a reference by Ferrara (1999) *J. Mol. Med.* 77:527-543, in which the VEGF-C's binding to both Flk1 and Flt1, and the different signaling pathways lead by Flk1 and Flt4 are described and particularly illustrated in Figure 1.

Because of the different and distinct biological properties of the FLt4 receptor compared to the VEGF receptors Flt1 and Flk1, and because VRP can bind to both Flt4 and Flk1, a method of using VRP to stimulate cell proliferation involving one receptor and its signaling pathway (e.g., Flk1) does not necessarily activate another receptor (e.g., Flt4) in the process. Thus, even though the VRP polypeptides of the present invention may share sequence identity to those disclosed in the '540 patent, the methods of administrating polypeptides speculated in the '540 patent based on the VEGF/VEGF receptor functions do not possess as an inherent element the stimulation of tyrosine phosphorylation of the Flt4 receptor. It has been well established that inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency. *Continental Can Co. USA, Inc. v. Monsanto Co., supra* at 1749.

For the reasons stated above, the '540 patent does not inherently teach the methods of stimulating Flt4 phosphorylation or the methods of promoting growth of Flt4-expressing endothelial cells as claimed in the present application. Applicants respectfully request the rejection under 35 U.S.C. §102(e) be reconsidered and withdrawn.

Applicants believe that the subject application is now in compliance with the requirements of 35 U.S.C. §112 and §102, and respectfully request an early Notice of Allowance be issued. The Examiner is invited to telephone the undersigned attorney at (650) 225-8674 to discuss any further issues and/or suggestions. Applicants will be pleased to submit documents necessary to advance this application to issuance.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extension of time and authorizes the

Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Genentech, Inc.'s Deposit Account No. 07-0630. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,
GENENTECH, INC.

Date: January 16, 2002

By: Steven X. Cui
Steven X. Cui
Reg. No. 44,637
Telephone: (650) 225-8674

Version with Markings to Show Changes Made

In the Claims:

Claims 58-64 have been canceled, and claim 40 has been amended as follows:

40. (Amended) A method for stimulating the tyrosine phosphorylation of a Flt4 tyrosine kinase receptor in a Flt4-expressing cell, comprising contacting the cell with ~~an effective amount of~~ a composition comprising a polypeptide comprising the amino acid residues 21 to 49 of SEQ ID NO:3, in an amount effective to stimulate the tyrosine phosphorylation of said Flt4 tyrosine kinase receptor.